## REMARKS

Claims 1-3, 6-10 and 13-15 have been rejected under 35 USC 103 over Maa, and claims 1, 4, 5, 11 and 12 under 35 USC 103 over Maa in view of Samaritani and Fujioka. Both of these rejections are respectfully traversed.

The present invention relates to a pharmaceutical composition which contains a solid intimate mixture of human growth releasing factor (GRF) and a stabilizing amount of saccharose or to a solution formed by reconstituting the solid mixture, and to a process of forming a lyophilizate. The claimed invention is not rendered obvious by the references applied in the outstanding Office Action.

The background in the present application likewise acknowledges that GRF requires stabilization. It points out that the available literature teaches that GRF suffers from chemical degradation in aqueous solution, primarily at the 8 position amino acid (Asn) and that the main hydrolytic reactions represent rearrangement of the amino acid (Asp) at the 3 position, cleavage of the bond between the 3 and 4 amino acids (Asp and Ala), and deamination and rearrangement of the Asn amino acid at position 8. The application also points out that commercially available hGRF in lyophilized formulations is stabilized with mannitol.

The references of record as well as the background of the invention teach that GRF requires stabilization, that mannitol has been found suitable and what needs to be protected is either the methionine at position 27, the Asn at position 8, the Asp at position 3 and the bond between the Asp and Ala positions 3-4. It is also indicated that finding a suitable stabilizer is fought with difficulties. There is no teaching or suggestion in these references or in the application background suggesting the use of saccharose as a stabilizer.

The newly cited Maa reference relates to making spray freeze dried proteins. As is apparent from the entire specification and claims, Maa is concerned with the general method rather than stabilizing any particular "therapeutic protein". It is also apparent from the description begin at column 6, line 33, than any know therapeutic protein, polypeptide and/or peptide can be employed in the method of this reference. Among the 34 specific "proteins" mentioned is GRF although this is not one of the preferred "proteins". Maa teaches that the formulations can be prepared without the use of excipients, i.e., protectants (column 3, lines 58-60) or can be prepared with the use such excipients. As to the excipients, Maa teaches that virtually any known excipient can be used and specifically identifies thirty-six excipients, some of which are as broad as a general class of materials (e.g., "surfactants"), and further teaches that combinations of excipients can be used. The number of combination and permeations of "proteins" and excipients runs well into the millions. Other than in the working examples which are concerned with recombinant anti-IgE monoclonal antibody, DNase and IgF, Maa does not teach or suggest any particular association of a "protein" with any given excipient. Maa is thus a shotgun disclosure from which the "likelihood of producing a composition such as here claimed from a disclosure such as shown by the [reference] patent would be about the same as the likelihood of discovering the combination of a safe from a mere inspection of the dials thereof." *In re Luvisi*, 144 USPQ646 or in CCPA 1965 (Ex parte Garvey 41 USPQ 583, 584, with emphasis by the Board of Appeals).

A person skilled in the art if motivated to try (and it is respectfully submitted there is no motivation) would spend untold hours of experimentation to test every excipient listed by Maa in varying amounts before having the possibility of arriving at a

stabilizing amount of saccharose as used in the present invention. Maa does not hint that saccharose is more effective than other excipients found in the art and provides no guidance which would lead one to select saccharose from the long list of excipients possible.

Beyond the foregoing, it is significant that Maa lists mannitol as possible excipient (column 8, line 31) in that mannitol was known in the art, prior to the present invention, to be the best stabilizer for GRF. As will be discussed below, the fact that saccharose provides a stability which is better than mannitol is clearly surprising and unexpected.

The Samaritani reference is explicitly limited to human growth hormone (HGH). However, GRF is very different from HGH. The reference does teach that saccharose can stabilize HGH but Samaritani does not teach or suggest that the saccharose can stabilize any other protein. Moreover, what requires stabilization in GRF is the amino acid Met at position 27, the amino acid Asp at position 3, the Asp - Ala bond at connecting positions 3-4 and the amino acid Asn at position 8 (application page 1, line 28 to page 2, line 7; see also, Fujioka column 1, lines 43-44). Obviousness is a conclusion which must have a factual basis, *In re Lee*, 277 F.3d 1338, 61 USPQ2d 1430 (Fed Cir. 2002)("common knowledge" and "common sense" not a substitute for evidence); *Ex Parte Haymond*, 41 USPQ2d 1217 (BPAI)(examiner has duty to supply factual basis for rejection); *In re Burt*, 365 F.2d 115, 148 USPQ 548 (CCPA 1966)(silence not a proper substitute for an adequate disclosure of facts from which a conclusion of obviousness may justifiably follow). The required factual basis is lacking here. No

attempt has been made to establish that HGH has these amino acids at these positions[1] and, therefore, there is no factual basis in the record for contending saccharose will stabilize anything other than HGH.

Moreover, no motivation for combining this reference with Maa has been advanced other than that Samaritani teaches use of saccharose in connection with "highly purified proteins". But his attempt at justification crosses the line at which simplification for description purposes improperly becomes a modification of the disclosure. *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 220 USPQ 97 (Fed. Cir. 1983). The fact that the references can be manipulated using hindsight does not satisfy the Examiner's burden of establishing a prime facie case of obviousness. *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). That saccharose may stabilize HGH does not suggest it will stabilize something else, and particularly that it will stabilize GRF.

Fujioki has been cited to teach lyophilisation of a composition containing 10mg/vial of GRF and glycine or human serum albumin. It teaches that GRF is rather unstable and hardly preservable in a solution. It further teaches that lyophilisation is not satisfactory because there is significant reduction in the titre when preserved at room temperature for a long period of time or exposed to heating, humidification or light as a result of the methionine at position 27 of the amino acids forming GRF being oxidized. Addition of antioxidants such as L-ascorbic acid had been unsatisfactory (col. 1, lines 36-48). The reference teaches that after strenuous efforts to overcome the problem, it was determined that human serum albumin or glycine can be used as a stabilizer. But there is no teaching or suggestion in this reference that saccharose can be used as a effective stabilizer for GRF. Quiet to the contrary, the reference implies that

finding an effective stabilizer for GRF is quite difficult. To rely on this reference not for what it says but for the proposition that GRF can be stabilized is nothing more, and nothing less, than an invitation to experiment. Obvious to try does not satisfy the requirements of Section 103.

Beyond all of the foregoing, it is respectfully submitted that the evidence which is in the record that saccharose acts in a different way than GRF or GRF plus mannitol establishes the patentability of the instant invention. In this connection, the Examiner's attention is respectfully invited to Tables 1 - 3 of the present application. In Tables 1-3, formulations 1 and 2 contain mannitol while formulation 3 contains saccharose. Table 2 shows that with mannitol (formulations 1-2), the pH increased over the 4 weeks of the study whereas the formulation containing saccharose did not increase from the initial value. Table 3 shows that the peptide purity of the mannitol containing compositions decreased by about 2% or more over the 4 weeks of the study whereas the saccharose containing formulation lost only 0.2% over the same period of time. These results show that the formulation containing saccharose presented a better stability profile when compared to formulations containing mannitol or mannitol/phosphate buffer. Mannitol is a known stabilizer for GRF and therefore the results achieved with mannitol present are necessarily better than those with native GRF. The fact that saccharose provided a stability which is better than mannitol stabilized GRF is clearly surprising and unexpected when viewed in light of the conclusion in the Office Action that native GRF or GRF plus mannitol would be expected to behave in the same manner as with saccharose. Accordingly, the claimed invention does have greater than the expected properties.

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[1] In actual fact, HGH does not have these amino acids at these positions -- the amino acid at the 3 position

In view of the foregoing considerations, applicant believes the pending application is in condition for allowance. The early issuance of a Notice of Allowance is respectfully solicited.

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Respectfully submitted,

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is Thr, at 4 is Ile, at 8 is Arg and at position 27 is Ser. See, e.g., US 6,348,444 at column 4, lines 40-46.